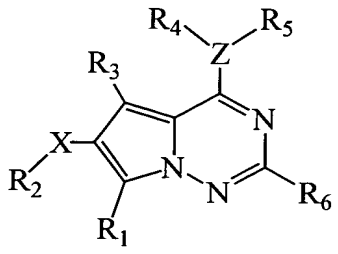
CLAIMS

We claim:

1. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



(I)

or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH_2;

X is selected from $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halogen, nitro, and cyano, or X is absent;

Z is selected from O, S, N, and CR_{20}, wherein when Z is CR_{20}, said carbon atom may form an optionally-substituted bicyclic aryl or heteroaryl with R_4 and R_5;

R_1 is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro, or cyano;

R_2 is selected from:

a) hydrogen, provided that R_2 is not hydrogen when X is $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, or $-NR_{10}SO_2-$;

b) alkyl, alkenyl, and alkynyl optionally substituted with up to four R_{26} or pentafluoroalkyl;

c) aryl and heteroaryl optionally substituted with up to three R_{27}; and

d) heterocyclo and cycloalkyl optionally substituted with keto (=O), up to

three R_{27}, and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or

e) R_2 is absent if X is halogen, nitro or cyano;

(i) R_4 is substituted aryl, aryl substituted with $NHSO_2$alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and

R_5 is hydrogen, alkyl, or substituted alkyl, except when Z is O or S, R_5 is absent, or alternatively,

(ii) R_4 and R_5 taken together with Z form an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl;

R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

R_{10} and $R_{11}$are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;

R_7, R_8, R_{21}, R_{24}, and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocylco, and substituted heterocyclo;

R_{20} is hydrogen, lower alkyl, or substituted alkyl, or R_{20} may be absent if the carbon atom to which it is attached together with R_4 and R_5 is part of an unsaturated bicyclic aryl or heteroaryl;

R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

R_{26} is selected from halogen, trifluoromethyl, haloalkoxy, keto (=O), nitro, cyano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, =N-OH, =N-O-alkyl; aryl optionally substituted with one to three R_{27}; cycloalkyl optionally substituted with keto(=O), one to three R_{27}, or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto (=O), one to three R_{27}, or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7}cycloalkyl, and C_{3-7}heterocycle, or may be taken together to form a C_{3-7}heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted

with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy; and

R_{27} is selected from alkyl, R_{32}, and C_{1-4}alkyl substituted with one to three R_{32}, wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7}cycloalkyl, and heterocycle, or may be taken together to form a C_{3-7}heterocycle.

2. The method of claim 1 comprising administering to the patient at least one compound having the formula (I), or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_3 is methyl, $-CF_3$, or $-OCH_3$;

X is selected from $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-SO_2NR_{10}-$, and $-C(=O)NR_{10}-$, or X is absent;

Z is N;

R_2 is hydrogen, C_{2-6}alkyl, C_{1-4}alkyl substituted with up to four R_{26}, pentafluoroalkyl, or aryl or heteroaryl optionally substituted with up to two R_{27};

R_4 is phenyl substituted with one R_{12} and zero to three R_{13};

R_5 and R_{10} independently are selected from hydrogen and lower alkyl;

R_{12} is carbamyl, sulfonamido, arylsulfonylamine, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or alkylsulfonylamine;

R_{13} at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)$alkyl, $-OC(=O)$alkyl, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-R_{17}, $-NHSO_2$-alkyl, $-SO_2NHR_{17}$, $-CONHR_{17}$, and

$-NHC(=O)NHR_{17}$;

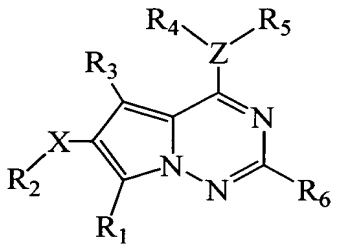
R_{14} is hydrogen, alkyl, or aryl;

R_{15} is hydrogen or alkyl;

R_{16} is hydrogen, alkyl, aralkyl, or alkanoyl; and

R_{17} is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl.

3. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



(I)

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH_2;

X is selected from $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halogen, nitro, and cyano, or X is absent;

Z is O, S, N, or CR_{20};

R_1 is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro, or cyano;

R_2 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, or heterocycloalkyl, or substituted heterocycloalkyl, or when X is halo, nitro or cyano, R_2 is absent, provided that

R_2 is not hydrogen when X is $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, or $-NR_{10}SO_2-$;

R_4 is substituted aryl, aryl substituted with $NHSO_2$alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring system;

R_5 is hydrogen, alkyl, or substituted alkyl, except that when Z is O or S, R_5 is absent;

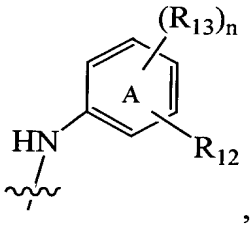
R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

R_7, R_8, R_{10}, R_{11}, R_{21}, R_{24}, and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R_{20} is hydrogen, lower alkyl, or substituted alkyl; and

R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo.

4. The method of claim 3 comprising administering to the patient at least one compound of formula (I), in which R_4 and R_5 taken together with Z form:



,

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_{12} is attached to any available carbon atom of phenyl ring A and is selected from carbamyl, sulfonamido, arylsulfonylamine, and ureido, each of which is optionally substituted with up to one of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or C_{1-4}alkylsulfonylamine;

R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)$alkyl, $-OC(=O)$alkyl, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2-$

aryl-R_{17}, $-NHSO_2C_{1-4}$alkyl, $-SO_2NHR_{17}$, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;

R_{14} is hydrogen, alkyl, or aryl;

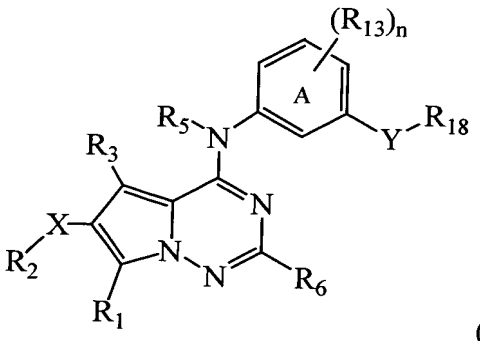
R_{15} is hydrogen or alkyl;

R_{16} is hydrogen, alkyl, aralkyl, or alkanoyl; and

R_{17} is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl; and

n is 0, 1, 2 or 3.

5. The method of claim 3 comprising administering to the patient at least one compound having the formula (II):



(II),

or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R_3 is methyl or CF_3;

X is $-C(=O)NR_{10}-$, $-NR_{10}C(=O)-$, $-C(=O)-$, or $-CO_2-$;

R_1 is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, halogen, nitro, or cyano;

Y is $-C(=O)NH-$, $-NHC(=O)NH-$, $-NHSO_2-$, or $-SO_2NH-$;

R_{10} is hydrogen or lower alkyl;

R_{18} is selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to three R_{19}, except that when Y is $-NHSO_2-$, R_{18} is C_{1-4}alkyl, aryl or aryl substituted with R_{19};

R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)$alkyl, $-OC(=O)$alkyl, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-R_{17}, $-NHSO_2C_{1-4}$alkyl, $-SO_2NHR_{17}$, $-CONHR_{17}$, and

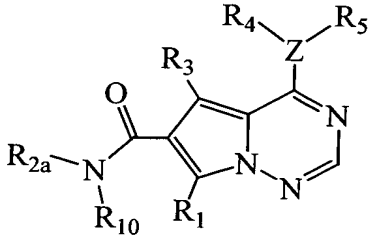
$-NHC(=O)NHR_{17}$;

R_{14}, R_{15}, R_{16} and R_{17} are hydrogen or alkyl;

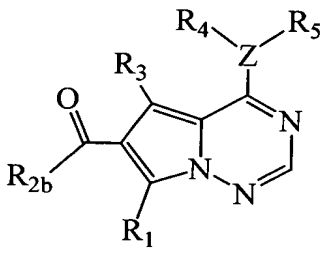
R_{19} at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, and aryloxy, wherein each group R_{19} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and

n is 0, 1 or 2.

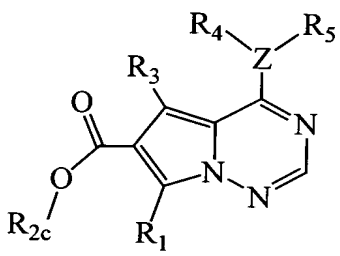
6. The method of claim 3, comprising administering to the patient at least one compound having the formula (Ia), (Ib), or (Ic):



(Ia)



(Ib)



(Ic)

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_3 is methyl or CF_3;

R_{2a} and R_{2c} are independently selected from hydrogen, C_{2-6}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, benzyl, and substituted benzyl;

R_{2b} is heterocyclo or substituted heterocycle; and

R_{10} is hydrogen or lower alkyl.

7. The method according to claim 1 wherein the one or more conditions associated with p38 kinase are selected from inflammatory disorders.

8. The method of claim 7, in which the inflammatory disorder is selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, diabetes, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, atherosclerosis, and arthritis including rhematoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis.

9. The method according to claim 1 wherein the one or more conditions associated with p38 kinase are selected from autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

10. The method according to claim 1 wherein the one or more conditions associated with p38 kinase are selected from edema, analgesia, fever, and pain.

11. The method according to claim 10 wherein the pain is selected from neuromuscular pain, headache, pain caused by cancer, dental pain, and arthritis pain.